

## COMMENTARY

# Coenzyme Q<sub>10</sub> deficiency in septic shock patients

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See related research by Donnino et al., <http://ccforum.com/content/15/4/R189>

### Abstract

Donnino and colleagues provide new insights into the field of oxidative stress and mitochondrial dysfunction during septic shock. These authors suggest a coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>) deficiency in patients with septic shock. Larger prospective observational trials measuring CoQ<sub>10</sub> in patients with septic shock are required to confirm the possibility of CoQ<sub>10</sub> depletion. This study is a new step toward a study testing CoQ<sub>10</sub> as a potential therapeutic agent for patients with septic shock.

In the previous issue of *Critical Care*, Donnino and colleagues [1] suggest a coenzyme Q<sub>10</sub> (CoQ<sub>10</sub>) deficiency in patients with septic shock. This study provides new insights into the field of oxidative stress and mitochondrial dysfunction during septic shock. Though extensively studied, the pathophysiology of sepsis-associated multi-organ failure (MOF) remains unknown. Sepsis is characterized by a systemic dysregulated inflammatory response and oxidative stress. One postulated mechanism is a set of changes in mitochondrial function with an inhibition or a dysfunction of the mitochondrial respiratory chain and a decrease of oxygen use [2]. A large body of evidence supports a key role of excessive production of reactive oxygen species in mitochondrial dysfunction and cellular injury during the various phases of sepsis (early- and late-phase MOF) [3,4]. Understanding the precise effect of sepsis on the mitochondrial function and the involvement of mitochondria in the development of MOF is fundamental.

CoQ<sub>10</sub>, also known as ubiquinone, plays a crucial role in the mitochondrial respiratory chain for ATP production. CoQ<sub>10</sub> is a lipophilic mobile electron carrier that is located in the inner mitochondrial membrane. CoQ<sub>10</sub>

receives electrons from complex I (NADH dehydrogenase) and complex II (succinate dehydrogenase) (reduction of ubiquinone to ubiquinol). Complex III (coenzyme Q-cytochrome c reductase) accepts electrons from ubiquinol and passes them to cytochrome c. CoQ<sub>10</sub> has been reported to have the ability to act as an effective antioxidant. Ubiquinone prevents peroxidation damage to cell membranes, regenerates  $\alpha$ -tocopherol, and maintains thiol levels. CoQ<sub>10</sub> is also a cofactor for uncoupling proteins. Finally, CoQ<sub>10</sub> plays a role in the control of mitochondrial transition pore opening, which is involved in apoptosis.

Several studies suggest an important role of CoQ<sub>10</sub> deficiency in neurodegenerative conditions such as Parkinson disease, Friedreich ataxia, and Huntington chorea and a benefit of oral supplementation [5]. In addition, CoQ<sub>10</sub> deficiency could play a role in the pathogenesis of heart failure. Recently, McMurray and colleagues [6] reported that a low serum CoQ<sub>10</sub> concentration was associated with worse outcomes in heart failure. It is important to note that, in that study, CoQ<sub>10</sub> was a marker of more advanced disease but that low plasma coenzyme CoQ<sub>10</sub> was not an independent predictor of prognosis.

So if there is a deficit in CoQ<sub>10</sub> during sepsis, the drug could be used in the prevention and treatment of sepsis-associated MOF to boost mitochondrial function and to mitigate cellular damage caused by oxidative stress. Until now, only animal models have been used to test the impact of CoQ<sub>10</sub> on the consequences of sepsis. Injection of CoQ<sub>10</sub> into the rostral ventrolateral medulla (medullary origin of sympathetic vasomotor tone) of rats diminished mortality and lipopolysaccharide-induced hypotension during exposure to lipopolysaccharide [7]. Lowes and colleagues [8] reported that MitoQ, an antioxidant this is selectively targeted to mitochondria and that comprises the lipophilic triphenylphosphonium cation covalently bound to ubiquinol, was able to limit oxidative stress, maintain the mitochondrial membrane potential, and prevent mitochondrial damage (endothelial cell model of sepsis) and acute liver and renal dysfunction (rat model of sepsis). In rat and mouse models of sepsis induced by endotoxin injected intraperitoneally, Supinski and colleagues [9] demonstrated that MitoQ prevented endotoxin-induced reductions in cardiac pressure-generating capacity, systolic

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pressure-diastolic relationship, and mitochondrial respiration rates. These authors found that MitoQ prevented the endotoxin-induced increase of cardiac levels of active caspases 9 and 3.

In this context, Donnino and colleagues [1] provide useful new information. They report that CoQ<sub>10</sub> levels of patients with septic shock are significantly lower than those of healthy controls. This result is interesting because it is the first report of low CoQ<sub>10</sub> levels in patients with septic shock. A major point to be considered in the interpretation of these low CoQ<sub>10</sub> levels is the set of changes in its major carriers, the low- and high-density lipoproteins, because the levels of these carriers can be affected by sepsis. The main limitation of this study is that it is a *post hoc* analysis of a prospective randomized trial of simvastatin versus placebo in patients with septic shock. As several studies have reported that patients treated with statins showed significant decreases in plasma/serum CoQ<sub>10</sub> [10], it could be argued that the observed low CoQ<sub>10</sub> levels are due to the simvastatin group. But there was no significant difference in change in mean CoQ<sub>10</sub> between randomization groups. However, as mentioned by the authors, the sample size for this study is small and larger prospective observational trials measuring CoQ<sub>10</sub> in patients with septic shock are required. But do these low CoQ<sub>10</sub> levels imply CoQ<sub>10</sub> supplementation in patients with sepsis? While we share the enthusiasm for CoQ<sub>10</sub> supplementation and mitochondria-targeted CoQ<sub>10</sub> as putative therapies in sepsis, low CoQ<sub>10</sub> levels could be associated with greater disease severity without playing an important mechanistic role in the pathophysiology of sepsis. This question can be definitively answered only by appropriately designed clinical trials testing the therapeutic efficacy of CoQ<sub>10</sub> supplementation or mitochondria-targeted CoQ<sub>10</sub>.

In conclusion, Donnino and colleagues [1] provide original data suggesting a CoQ<sub>10</sub> deficiency in patients with septic shock. This is an exciting hypothesis in the field of oxidative stress and mitochondrial dysfunction during septic shock. This study is a new step toward a study testing CoQ<sub>10</sub> as a potential therapeutic agent for patients with septic shock.

#### Abbreviations

CoQ<sub>10</sub>: coenzyme Q<sub>10</sub>; MOF, multi-organ failure.

#### Competing interests

The authors declare that they have no competing interests.

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Published: 4 October 2011

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doi:10.1186/cc10429

Cite this article as: Dupic L, et al.: Coenzyme Q<sub>10</sub> deficiency in septic shock patients. *Critical Care* 2011, **15**:194.